UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,113	10/17/2001	Gabriel Lopez-Berestein	UTSC:660US/SLH	9331

7590 07/28/2005

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
Suite 2400
600 Congress Avenue
Austin, TX 78701

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/982,113
Filing Date: October 17, 2001
Appellant(s): LOPEZ-BERESTEIN ET AL.

David L. Parker
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11-3-04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

According to appellant, claims 139 and 140 are separately patentable.

(8) Claims Appealed

Claims appealed are 138-141.

(9) Prior Art of Record

5,811,119	MEHTA et al	9-1998
5,008,291	MINTON et al	4-1991

6,093,706 ZELIGS 7-2000

Ulukaya, E et al. "Fenretinide and its relation to cancer" Cancer Treatment Reviews, vol. 25, (1999), pp. 229-235.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 138-141are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (5,811,119) in view of Ulukaya (Cancer Treatment Reviews, 25, pp. 229-235, 1999 of record.

Mehta discloses a method of treatment of cancer using liposomal retinoid. The liposomes are made from the claimed combination of dimyristoyl phosphatidyl choline and the intercalation promoter, soybean oil (note the abstract, col. 3, lines 16-21; col. 6, line 24 through col. 7, line 31; Examples, in particular Examples 1, 5, 6 and 9. Although in Mehta, the invention is exemplified using retinoic acid, according to Mehta on col. 2, line 60 et seq., the term includes all retinoids.

Mehta however, does not specifically teach 4-hydroxyphenyl retinamide.

Ulukaya while disclosing the relationship between 4 hydroxyphenyl retinamide and cancer, teaches that this retinoid has fewer side effects compared to naturally occurring retinoids and that it seems to induce apoptosis via different pathway from classical retinoids (note the abstract).

The use of 4-hydroxyphenyl retinamide as the specific retinoid in the teachings of Mehta would have been obvious to one of ordinary skill in the art since Mehta teaches the use of any retinoid and Ulukaya teaches that this retinoid has fewer side effects compared to naturally occurring retinoids and induces apoptosis via different pathway from classical retinoids. The mode of administration recited in the added claims is deemed to be a manipulatable parameter. The criticality of the ratios and the amounts of water in the added claims is not readily apparent to the examiner in the absence of showing of unexpected results.

Applicants' arguments have been fully considered, but are not found to be persuasive. Appellant argues that the principle reference of Mehta fails to teach or suggest the use of DMPC and water to form liposomes. According to appellant, Mehta's example 1 describes the preparation of liposomal all trans-retinoic acid and that in the paragraph beginning at column 7, line 54 of Mehta, it is described that the retinoic acid is comprised in t-butanol, and that the butanol-solubilized RA is then added to the dried lipid film to form the liposomes and not water to form liposomal retinoid. Appellant further argues that the examiner has not shown that the re-suspending already formed liposomes in an aqueous solution results in the introduction of water into the bilayer. According to appellant it does not. These arguments are not found to be persuasive. First of all, as pointed out before, liposomes are bilayer structures formed by specific orientation of the phospholipids when hydrated with water or aqueous medium. Dissolving the phospholipids in an organic solvent, removing the organic solvent and adding an aqueous medium and either vortexing or sonicating to form liposomes is a

conventional method of preparation of liposomes. If the compound is lipophilic, it is added to the organic solvent containing the phospholipid and if it is hydrophilic it is added to the aqueous medium in the conventional method. Without an aqueous medium **liposomal structures do not form at all.** Secondly, what is disclosed by Mehta is the typical liposome preparation technique except that Mehta adds t-butanol twice and removing it twice before adding the aqueous medium to form liposomes. The examiner directs the board's attention to page 33, lines 15-18 of the specification, which recites the same classical method of preparation of liposomes, that is, "hydration of the dried lipids with an aqueous medium". Appellant argues that "re-suspending already formed liposomal/drug in an aqueous (medium) results in water going into the interior of the liposome, not into the lipid bilayer. This argument is not found to be persuasive since instant claims do not recite this limitation. Instant claim 138 recites, 'lipid material comprises dimyristoyl phosphatidylcholine (DMPC) and water" implying, "liposomes having DMPC and water'. With regard to the surprisingly higher incorporation of active agent in water containing liposomes, the examiner points out that as noted from Example 1, water-t-butanol mixture is used during the preparation of the liposomes which is then freeze-dried which process removes water whereas instant claims recite "composition comprises from 1 to 10 % water" and not liposomes themselves and the claims are not method of preparation claims. The amount of aqueous medium added therefore, depends upon the mode of administration of the composition, for e.g., one would add more aqueous medium if the method of administration is intravenous. Furthermore, a careful examination of Table 2 pointed out by appellant indicates an

improper comparison between the groups. In the method of preparation of lipid powder without water in t-butanol, the ratio of 4-HPR-lipid is 1:17 whereas, in the groups where in water:t-butanol mixture was used, the ratios are either 1:10 or 1:5. Furthermore, it is unclear whether the values are patentably significant since there is no statistical evaluation. The examiner respectfully points out to the board the importance of keeping all the parameters the same while comparing the groups especially in view of Mehta's teachings of variations in encapsulating efficiencies and even up to 90.7 percent encapsulation in Table 1 on col. 8.

Appellant argues that Ulukaya teaches away since he teaches that 4-HPR has properties that distinguish(es) it from naturally occurring retinoids, including the fact that it apparently exerts its clinical effects by a different pathway from classical retinoids. First of all, Ulukaya only speculates the mechanism of action. In the abstract section, the statement made by Ulukaya is "Although the mechanism by which Fenretinide acts is not entirely known it is considered to be a promising drug ----". Irrespective of the mechanism by which acts, it is the position of the examiner that one of ordinary skill in the art would be motivated to use 4-HPR because of its ability to induce cell death even in ATRA –resistant cell lines as taught by Ulukaya. Applicant argues that Mehta proposes the use of lipid formulations is for the purpose of 'reduced toxicity' and yet Ulukaya teaches that the 4-HPR in and of itself solves the toxicity problem and therefore there is no motivation from Ulukaya or Mehta to provide a lipid based formulation of 4-HPR. This argument is not found to be persuasive since reduction of drug toxicity by is only one of Mehta's reasons for using liposomes. On col. 2, lines 5-18, Mehta clearly

states that liposomal format is a useful one for controlling the topography of drug distribution in vivo. Mehta further states, "This, in essence, involves attaining a high concentration and/or long duration of drug action at a target (e.g. a tumor) site where beneficial effects may occur, ----". Applicant's arguments thus, are not found to be persuasive.

2. Claims 138-141are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta (5,811,119) in view of Minton (5,008,291) or Zeligs (6,093,706) by themselves OR vice versa: that is, Minton (5,008,291), or Zeligs (6,093,706) in view of Mehta (5,811,119).

Mehta discloses a method of treatment of cancer using liposomal retinoid. The liposomes are made from the claimed combination of dimyristoyl phosphatidyl choline and the intercalation promoter, soybean oil (note the abstract, col. 3, lines 16-21; col. 6, line 24 through col. 7, line 31; Examples, in particular Examples 1, 5, 6 and 9. Although in Mehta, the invention is exemplified using retinoic acid, according to Mehta on col. 2, line 60 et seq., the term includes all retinoids.

Minton in 291 teaches that a combination method for achieving a very high degree of chemotherapeutic activity through a synergistic combination of a low sub optimal dose of calcium glucarate (anti-carcinogen) and a sub optimal dose of 4-hydroxyphenyl retinamide. One of the cancers studied is mammary cancer (abstract; col.4, line 23 through col. 6, line 41; Examples). What is lacking in Minton is the use of liposomes as the sustained release carriers for the combination. However, Minton on

col. 13, lines 17 and 18 suggests the use of sustained or continuous release formulations.

Zeligs teaches a combination treatment of diseases such as squamous cell carcinoma using 4-hydroxyphenyl retinamide and dehydroepiandrosterone. The combination is administered in the form of liposomes (abstract, col. 5, line 28; col. 6, line 60; Example 3; claims 46 and 55). What are lacking in Zeligs' teachings are the use of DMPC as the phospholipid and the inclusion of soybean oil.

It would have been obvious to one of ordinary skill in the art to use 4-hydroxyphenyl retinamide as the specific retinoid in the teachings of Mehta since Mehta teaches the use of any retinoid and the references of Minton and Zeligs show the effectiveness of this retinoid in combination with other active agents which includes synergism as noted from Minton. Alternately, the use of liposomes containing DMPC and soybean oil of Mehta as the sustained release carriers for the formulations of Minton, or Zeligs would have been obvious to one of ordinary skill in the art since this combination of DMPC and the intercalation promoter, soybean oil is very effective for the delivery of retinoids in cancer treatment process as taught by Mehta. The mode of administration recited in the added claims is deemed to be a manipulatable parameter. The criticality of the ratios and the amounts of water in the added claims is not readily apparent to the examiner in the absence of showing of unexpected results.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed appellant's arguments pertaining to Mehta. Applicant appears to question the relevancy of Minton's disclosure to

DMPC/SO/water formulations. Applicant argues that Minton simply teaches that one can prepare sustained release formulations of the 4-HPR and calcium gluconate and it is hard to imagine how the preparation of a sustained release formulations of these two drugs would lead one of skill in the art to Mehta. The examiner disagrees with appellant. First of all, Minton teaches the efficacy of the same claimed compound, 4-HPR and suggestive of the use of sustained delivery formulations for the delivery of the compound and since liposomes are 'sustained release vehicles' one of ordinary skill in the art would certainly be motivated to use Mehta's liposomes which are used for retinoids which belong to the same group of claimed retinamide. The examiner respectfully points to the board that originally Minton was used to show the use of 4-HPR in combination with other anti-cancer agents for the synergistic effect for even the originally submitted claims which had combination of active agents, the reference is still applicable for the appealed claims which do not recite the combination.

Appellant agrees that Zeligs is the one reference that does refer generically to liposomal formulations of DHEA and retinoids such as 4-HPR, but argues that there is no basis for combining this teaching with Mehta per se to arrive at the presently claimed invention. According to appellant although there is some disclosure that concerns parenteral administration and disclosure that the systemic administration is to prevent the recurrence of squamous cell carcinoma, there is no disclosure that would suggest to one of skill in the art to select and use a DMPC/SO/water formulations. Furthermore, according to appellant, a very general disclosure such as Zeligs cannot render each and every cancer therapeutic methods using lipid formulations obvious. This argument is not

found to be persuasive since as appellant himself recognizes, Zeligs is suggestive of the efficacy of the claimed compound against cancer and also suggestive of the use of liposomes. If one were to follow appellant's rationale, then one could question appellant's claiming of 'treating a subject having cancer' when it is well-known in the art that there is no one single compound or composition which is able to treat all forms of cancer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK
July 11, 2005

Conferees

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Thurman Page:

JAMES M. SPEAR
PRIMARY EXAMINER
AU 1618

James Spear:

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
Suite 2400
600 Congress Avenue
Austin, TX 78701